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A novel mutation of DAX-1 (NR0B1) in a boy with X-linked adrenal hypoplasia congenita

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Introduction

DAX-1 (NR0B1) plays a key role in adrenal and reproductive development. It interacts with other nuclear receptors; however, its exact biological role remains unclear. In men most patients with X-linked adrenal hypoplasia congenita (AHC) present with acute adrenal failure. Onset of clinical manifestation can occur at any age, primary adrenal failure usually being the first sign, followed by puberty failure as a result of hypogonadotropic hypogonadism.
To date DAX-1 mutations have been found in more than 100 families or patients with X-linked AHC.

Conclusion

In any child presenting with recurrent vomiting acute adrenal failure has to be assessed. DAX-1 mutation must be considered when diagnosis of primary adrenocortical insufficiency is made, especially if there is a history of unexplained death of maternal male relatives. Furthermore, this report adds a novel mutation to the known DAX-1 variants and underlines the importance of genetic confirmation of the diagnosis to counsel the family and prevent future fatal outcomes.

Case report

We report the case of a 2.5-year-old boy who was brought to our emergency department with vomiting and progressive fatigue. He had a history of recurrent vomiting and increasing hyperpigmentation of the skin over 6 months. The diagnosis of acute adrenocortical insufficiency with salt wasting was made based on the clinical picture of severe fatigue and the laboratory results of decreased sodium, increased potassium, inadequately low cortisol and elevated ACTH (Tab. 1). The boy was transferred to our ICU for rehydration and substitution with hydrocortisone and sodium. Insulin was adequately low and growth hormone appropriately elevated ruling out other endocrine etiologies of the hypoglycemia.

After stabilization the patient was put on an oral regimen with hydrocortisone (14 mg/m^2/day) and fludrocortisone (0.1 mg/day), under which clinical signs normalized within a few days. Growth and psychomotor development have been normal since then.

Family history revealed unexplained death of 3 brothers of the mother during infancy. Additional laboratory evaluation excluded congenital adrenal hyperplasia (low 17-hydroxyprogesterone) and adrenoleukodystrophy (normal plasma concentration of very long-chain fatty acids). Negative 21-hydroxylase and adrenal autoantibodies made an autoimmune Addison disease very unlikely (Table 1). Finally direct sequencing of PCR fragments amplified from genomic DNA of the patient revealed the presence of a novel hemizygous mutation, c.870C>A in Exon 1, leading to the formation a premature stop codon (Figure 1). The parents were also screened and his mother was shown to be carrier of the same mutation. Functional studies demonstrated that the loss-of-function is not due to nonsense mediated decay (NSMD) and are currently aiming at the clarification of the interaction of the mutated DAX1 with its partner SF1 (NR5A1).

Table 1. Clinical and biochemical findings at presentation

	Values	Normal range
Weight, kg	11	
Height, cm	92	
Cortisol, nmol/l	1	171-526
17-OH-progesterone	<0.2	0.4-1.5
ACTH, pg/ml	6040	10-50
Sodium, mmol/l	121	135-145
Potassium, mmol/l	4.8	3.5-4.5
Glucose, mmol/l	2.5	3.7-5.6
Growth hormone, ng/ml	7.9	<8
Insulin, pmol/l	<4	<180
C-Peptid, pmol/l	<50	200-1400
pH	7.33	
pCO2	3.3	
HCO3	15.7	
BE	-11.9	

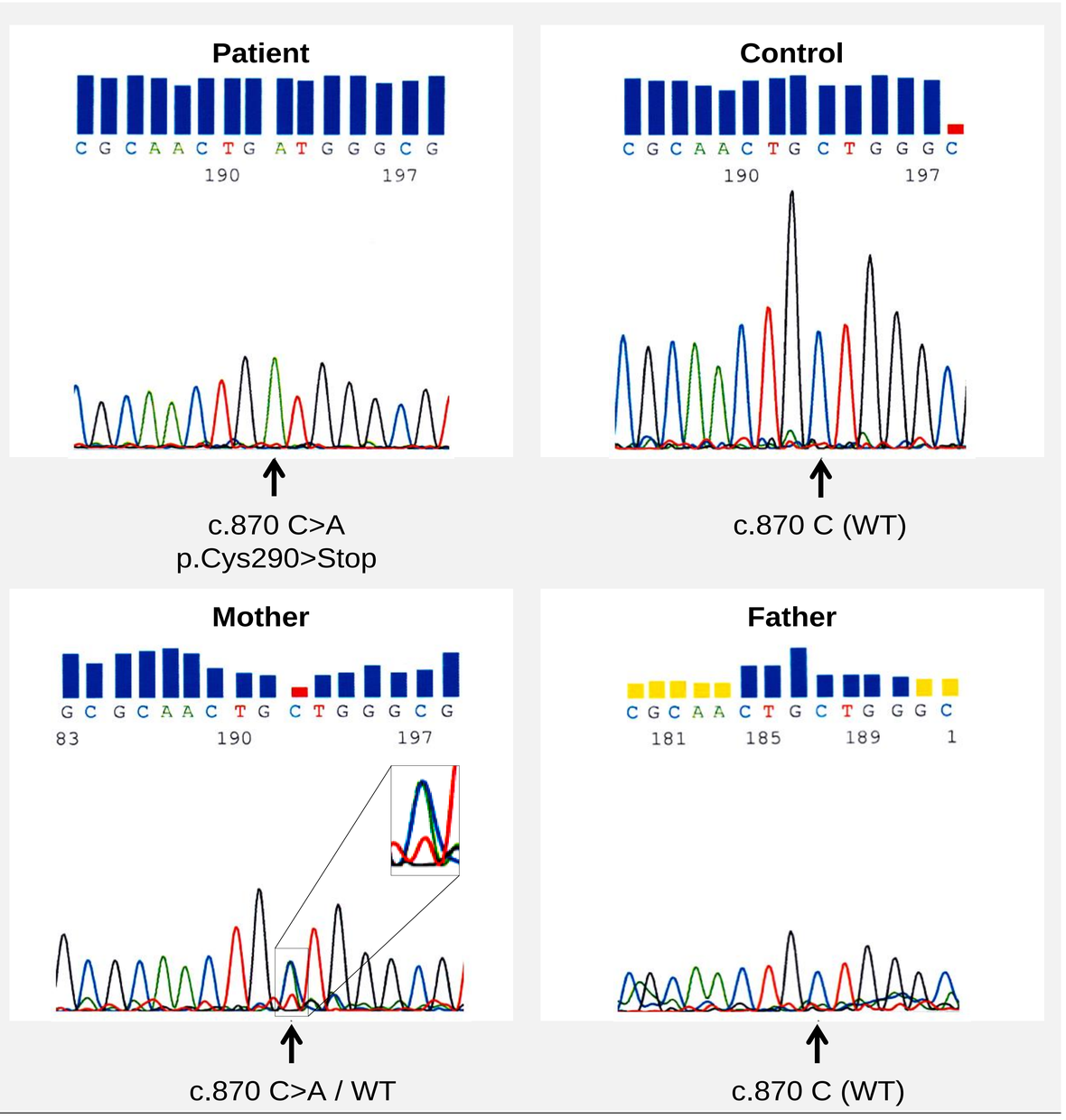

Figure 1. DNA sequences ►

The authors have nothing to disclose

55ESPE 65--P2
Adrenal
Karine Gerster
DOI: 10.3252/pso.eu.55ESPE.2016
Poster presented at: ESPE 2016 PARIS
PosterSessionOnline.com